ISSN: 0974-2115
Journal of Chemical and Pharmaceutical sciences

EFFECT OF POLYMERS ON SUSTAINED RELEASE OF DILITIAZEM-HYDROCHLORIDE MATRIX TABLET

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ABSTRACT

Diltiazem hydrochloride is a calcium channel blocker, antihypertensive agent and it is most widely used in the treatment of hypertension, arrhymias and angina pectoris. The approach of the present study was to make a comparative evaluation among these polymers and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The literature reviews shows that, the release of water-soluble drugs was higher than the drugs with lower solubility and the mechanism of release were changed with the nature and content of polymer in the matrix. The type of polymers used imparts a conspicuous effect on release mechanism. The present study aimed for sustained effect of Ethyl cellulose release characteristics of various hydrophilic polymer; HPMC, SCMC and Carbopol. The study revealed various facts regarding drug release from hydrophilic polymer matrix. Diltiazem being a soluble drug; the drug release depends on characters of matrix more than the drug characters. Hydrophilic polymer at 1:3 ratio of drug, polymer show high retarding effect hence the release of the drug from the matrix takes place gradually. The drug release mechanism reveals that it follow Anomalous case- II- non-fickian release, which means drug release rate controlled by both diffusion and dissolution.

KEY WORDS: Dilitiazem hydrochloride, hydroxy propyl methyl cellulose, Carbopol 932, SCMC, Ethyl Cellulose (EC), Microcrystallinecellulose.

1. INTRODUCTION

The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ of tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. The sustained release drug delivery system can be a major advance towards solving these two problems (Hiroyuki,2008). The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well. For this discuss, these dosage forms can be considered to release their active ingredients into absorption pool immediately. The absorption pool represents a solution of drug at the site of absorption, and the terms Kr, Ka and Ke are first-order rate constants for drug release, absorption and overall elimination, respectively (Amri and Sfar, 2008). Immediate release from a conventional dosage form implies that Kr>>>Ka or that observation of drug across a biological membrane, such as the intestinal epithelium, is the rate- limiting step in delivery of drug to its target. For non immediate release dosage form, Kr<<<Ka, that is, release of drug from the dosage form the rate limiting step. This causes the above kinetic to reduce to the following. Which are based on controlled of programmed drug delivery methods I the vicinity of target tissue, this undeniable fluctuation of drug levels (concentration) between toxic level and sub-therapeutic level can be greatly reduce(Muhammad khan,2006). This controlled drug-therapy offers a method for which therapeutic action in enhanced and the dangerous toxic level eliminate. With many drugs, the basis goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regiments is an important element in accomplished this goal (Jaber and Naser,2004). The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific tissue, while temporal delivery refers to controlling the rate of drug delivery(Pandey,2003).

2. MATERIALS AND METHODOLOGY

2.1 Materials: Diltiazem Hcl was obtained as a gift sample from Ranbaxy pharm Ltd, Gurgoan, New delhi, HPMC K_4M obtained from Arvind Laboratories Pvt Ltd, Carbopol 932 and Talc obtained from SD fine chem. Ltd, Sodium.CMC obtained from Dow Chemicals, Ethyl cellulose obtained from Colorcon, PVP and Magnesium Sterate obtained from Sisco research Lab Pvt. Other excipients and chemicals are used are of analytical grade.

2.2 Direct Compression: It is the economical approach since it is a basic two – step process (if components are of the proper particle size), involving only mixing and compressing and it avoids the most costly process of unit operations, drying (Parabakaran,2003). Hence it is the fastest, most direct method of tablet production and it has the potential to lead to the most bio-availability roduct. Initially Weighing raw materials followed by screening through sieve no: 60, mixing Drug, polymer and excipients then subjected to Direct Compression. Quantity sufficient for batch of 90 tablets was mixed thoroughly to ensure complete mixing. Tablets containing 120mg equivalent to Diltiazem HCl were compressed to a compaction force of 26KN and using 9.5mm round, flat and plain punches on a single stroke punching machine(Raghuram Reddy,2003). All ingredients except Magnesium Stearate were blended for 10 minutes. Magnesium stearate was added and the mix blended for an additional 5 minutes. Tablets were compressed by Direct Compaction using a Single Stroke punching machine(Bonferoni,2000). Diltiazem Hcl was mixed with polymers in different ratios such as drug: polymer ratio 1:3 along with different diluents

2.3 Evaluation of diltiazem Hcl matrix tablets: The formulation of diltiazem matrix tablet has been carried out and the following post- evaluation parameters such as Weight variation, Hardness, Friability, Content uniformity, Thickness, *In-Vitro* Dissolution and the results has been tabulated (Anurag,1998).

Table 1 Formulation of Diltiazem Hcl Matrix Tablets Using HPMC K_4M, Carbopol 932 polymer and SCMC polymer

Ingredients	Formulation Code														
	HA	HB	HC	HD	HE	CA	CB	CC	CD	CE	SA	SB	SC	SD	SE
Diltiazem HCl	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
HPMCK4M	360	360	360	360	360	--	--	--	--	--	--	--	--	--	--
Carbopol 932	--	--	--	--	--	360	360	360	360	360	--	--	--	--	--
SCMC	--	--	--	--	--	--	--	--	--	--	360	360	360	360	360
Ethyl Cellulose	5	10	15	20	--	5	10	15	20	--	5	10	15	20	--
PVP	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
MCC	65	60	55	50	70	65	60	55	50	70	65	60	55	50	70
Mg Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total mg	560	560	560	560	560	560	560	560	560	560	560	560	560	560	560

3. RESULTS

Diltiazem HCl release from HPMC formulations were found to be increasing with increase in EC contents. The HPMC at 1:3, drug; polymer ration has retarded drug release, only around 50% of drug is released after 8hrs. Formulation HB showed a maximum sustained release of 10mg of drug from EC. Carbopol, 1:3 ratio; shown a good retarding effect, 43% of drug is released after 8hrs; in presence of 5mg EC; the drug release is increased up to 42% but further increases in EC, level has retarded drug release. SCMC 1:3ratio, shown a retarding affects that 38% of drug after 8 hrs; in presence of EC; and an increase in EC content, drug release is retarded proportionately. When compared between HPMC, Carbopol and SCMC; sustaining effect is in order of Carbopol>SCMC>HPMC. Though all are hydrophilic polymers; retarding effect is more with Carbopol compared to others. Effect of EC on drug release is that in all cases, presence of 5mg of EC; has greatly increased drug release. Future increased has no effect in HPMC; Carbopol; where as in SCMC a proportional decreased in drug release with a increase in concentration of EC.

3.1 *In-Vitro* Dissolution Studies of Diltazem Hcl Matrix Tablet: Sustained release matrix tablets containing diltiazem HCL with Hydroxypropyl methyl cellulose, Carbopol and Sodium Carboxy methyl cellulose were prepared and *in vitro* dissolution studies were performed at 37±0.5ºC for 8 Hours at 100 rpm by using 0.1 NHCL and 6.8 PH Phosphate buffer as a dissolution medium according to USP.

4. CONCLUSION

From the study it is revealed that various facts regarding drug release from hydrophilic polymer matrix. Diltiazem being a soluble drug; the drug release depends on characters of matrix more than the drug characters.Hydrophilic polymer at 1:3 ratio; drug; polymer show a high retarding effect; but a little EC might

increase drug release or in other words, reduced or in other words, reduces retarding effect of hydrophilic polymer. The drug release mechanism Anomalous case- II- non-fickian diffusion, which means drug release rate controlled by both diffusion and dissolution.Retarding effect in order Carbopol> SCMC> HPMC. In all the formulations HA, SA, CA, where found to show a greater drug release compared to one without EC; The data's generated shall be used for developing a effective and ideal sustained release tablet for Diltiazem.

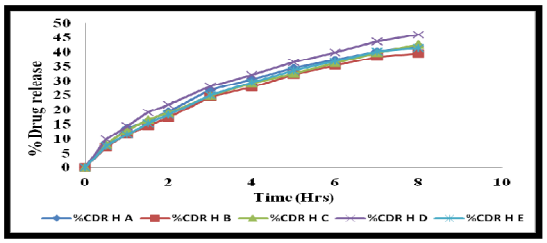
Table 2 Pre-formulation Studies of Diltiazem Hydrochloride

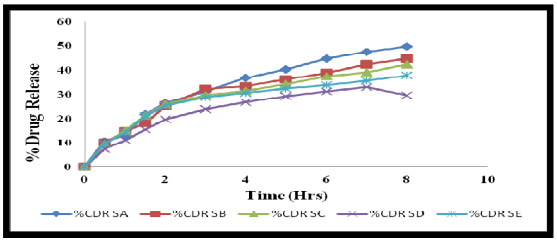
Properties	Observation
Color,odor, ppearance	White odorless crystalline powder
Solubility	Freely soluble in water, chloroform, sparingly soluble in alcohol and insoluble in ether
Bulk density	0.52g/cm^3
tapped density	0.75 g/cm^3
Hausner's ratio	1.95
Angle of repose	39.2^o
Melting point	210^{o}c with decomposition

Table 3 Comparative Dissolution Profile

%CDR	Time										
	0	0.5	1	1.5	2	3	4	5	6	7	8
HA	0	7.6	13.6	16.1	19.4	26.9	30.5	34.5	37.3	40.2	42.2
HB	0	7.15	11.5	14.5	17.2	24.6	27.8	32.3	35.3	38.3	39.6
HC	0	8.05	13	16.6	18.9	24.9	29.1	32.6	36.1	39.7	42.7
HD	0	9.8	14.3	19.1	21.8	28.2	32.1	36.5	39.9	43.7	46
HE	0	7.55	11.5	15.4	18.3	25.1	29.5	33.6	36.8	40.2	41.4
CA	0	7.6	13.55	16.05	19.35	26.85	30.5	34.45	37.3	40.15	42.2
CB	0	5.2	8.5	12	14.2	15.6	17.1	18.2	20.2	23	23.9
CC	0	5.75	9	11.815	14.05	15.45	17.125	18.425	19.685	21.19	22.6
CD	0	6.2	9.05	11.9	14.875	16.05	17.65	19.25	20.345	22	23.235
CE	0	5.85	8.74	11.8	13.85	15.3	16.97	18.535	20	21.1	22.58
SA	0	10.825	13.3	22	26.3	31.25	36.85	40.3	44.5	47.45	49.6
SB	0	10.1	14.8	18.21	25.45	32.3	33.55	36.3	38.955	42.3	44.5
SC	0	9.5	15.25	21.605	25.9	29.55	31.5	34.35	37.55	39.15	42.35
SD	0	7.605	11.2	15.7	19.8	23.85	26.7	29.25	31.3	33.1	29.6
SE	0	9.75	14.49	21.4	25.385	28.75	30.65	32.37	33.87	35.65	37.95

Figures: Comparative Dissolution Profiles





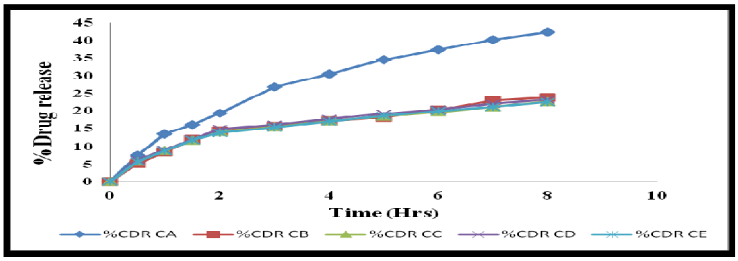


Table4 Regression Coefficients (R) Of Diltiazem HCl Release Data From Studies Matrices According To Different Kinetic Models

formulation code	zero-order		first-order		higuchi		kosermayer			
	R	k	r	k	r	k	r	k	n	order
HA	0.966	4.931	0.982	0.066	0.996	15.850	0.995	7.717	0.89	Zero Order
HB	0.972	4.746	0.985	0.062	0.995	15.110	0.997	7.079	0.9	SuperOrder
HC	0.974	4.863	0.989	0.065	0.997	15.490	0.999	7.719	0.87	Nonfickian
HD	0.968	5.231	0.986	0.073	0.998	16.800	0.999	8.705	0.85	Nonfickian
HE	0.973	4.968	0.987	0.072	0.995	15.815	0.998	7.320	0.9	SuperOrder
CA	0.996	4.939	0.982	0.066	0.996	15.850	0.995	7.716	0.89	Zero Order
CB	0.939	2.547	0.956	0.297	0.991	8.370	0.982	5.635	0.74	Nonfickian
CC	0.923	2.342	0.937	0.027	0.990	7.818	0.985	5.853	0.7	Nonfickian
CD	0.922	2.420	0.936	0.028	0.990	8.080	0.987	6.045	0.7	Nonfickian
CE	0.927	2.376	0.940	0.027	0.992	7.858	0.985	5.830	0.7	Nonfickian
SA	0957	5.706	0.980	0.082	0.995	18.470	0.988	9.300	0.88	Nonfickian
SB	0.940	4.950	0.963	0.068	0.991	16.240	0.988	9.060	0.84	Nonfickian
SC	0.927	4.497	0.952	0.061	0.990	14.950	0.980	9.150	0.8	Nonfickian
SD	0.909	3.603	0.923	0.045	0.978	12.070	0.979	7.435	0.8	Nonfickian
SE	0.898	3.903	0.924	0.051	0.979	13.440	0.971	9.100	0.76	Nonfickian

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